REMARKS

Claims 48, 50-56, and 58-75 are active in this application. Claims 48 and 56 have been amended to define the transactivating factor as the HIV tat transactivating factor. This amendment is supported by Claim 49, Claim 57, and the specification page 4, lines 24-27. No new matter is added by these amendments.

Applicants wish to thank Examiner Priebe for the helpful suggestion on page 3 of the Office Action and for withdrawing the rejections over Bromley alone or in combination with other documents.

In the outstanding Office Action there are two remaining issues.

The first is a rejection of Claims 48-75 under 35 U.S.C. § 112, first paragraph (written description). This rejection has been addressed by the amendments to Claims 48 and 56 submitted herein. Therefore, withdrawal of this rejection is requested.

The second issue is a rejection of Claims 56-67 under 35 U.S.C. § 112, first paragraph[1] which is based on the allegation that the methods of expressing a selected polynucleotide *in vivo* is not enabled. Applicants respectfully disagree and provide the following to support the enablement of these claims.

First, Applicants direct the Examiner's attention to MPEP § 2164.01 (c) which states:

> If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, **if any use is enabled** when multiple uses are disclosed, **the application is enabling for the claimed invention**.

[1] Reference to cancelled claim 47 in the rejection under 35 U.S.C. § 112, first paragraph on page 4 of the Office Action is believed to be a typographical error and therefore is not further discussed.

In the present case, the Office has already stated that the claimed invention is enabled for *in vitro* uses (page 4 of the Official Action). Therefore, the fact that *in vitro* uses are enabled confirms that the Claims 56-67 are enabled even if the method may also performed *in vivo*.

Furthermore, Applicants direct the Examiner's attention to MPEP § 2164.01(a) which cites *United States v. Telectronics, Inc.*: [2]"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."

Claim 56, and the claims dependent thereon, is directed to a method of expressing a selected polynucleotide in a cell. Here, there is no question that provided with the description in the application for making the vector and transferring the vector into a cell, whether *in vitro* or *in vivo,* one of skill in the art can express a selected polynucleotide without undue experimentation. While the specification does, in some instances, tie *in vivo* expression to therapy, the specification and the knowledge in the art provide alternative non-therapeutic uses as well.

Applicants have previously pointed to specific disclosures in the application which describe uses alternative to therapy for the expression of selected polynucleotides *in vivo*. The Examiner dismissed the embodiment described in Example 4 on page 69 stating that the description is "a prophetic example for assessing the claimed method as a therapy, which constitutes investigation on the invention rather than using the invention as a research tool." (page 5 of the Official Action). Applicants disagree.

How is a test to assess the ability of the selected polynucleotide to affect tumor growth not a research tool? This Example clearly provides to the skilled artisan the usefulness of the claimed expression construct to test the efficacy of EGFP and IL-2 and perhaps other

genes in mouse models of human cancer with the hope of identifying the best gene(s) for treatment.

As further support of the enablement of Claims 56-67, Applicants direct the Examiner's attention to the discussion in MPEP 2164.01(a) citing the Federal Circuit decisions of *In re Buchner*[3] and *Hybritech, Inc. v. Monoclonal Antibodies,, Inc.*,[4] which states: "A patent need not teach, and **preferably omits**, what is well known in the art." (emphasis added).

Consistent with the above discussion concerning other enabling uses of the claimed methods, Applicants note that there were numerous well-known uses in the art for expression constructs to express polynucleotides *in vivo* at the time the present application was filed. Even a cursory review of the literature available at that confirms this statement. Thus, in addition to the uses described in the application there are unquestionably other *in vivo* uses that are so well-known that, according to the Patent Office's published guidelines, should not be included in the specification.

Applicants attach hereto and summarize several examples of this knowledge. For the sake of brevity, only a few examples are provided.

1. Jiao et al (1992) *Exp. Neurol* 115:400-413 describe the use of an expression vector encoding a β-galactosidase reporter gene to assess the persistnace of the vector in rat brain cells *in vivo*.
2. Felgner et al (1995) *Ann N Y Acad Sci.* 772:126-39 describe the use of expression vectors to study the efficacy and utility of cationic liposomes to deliver genes *in vivo*.

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[2] 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).
[3] 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).
[4] 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

3. Wolff et al (1990) *Science* 247:1465 describe the use of expression vectors to assess gene expression in a mouse when the expression vector is directly injected into the skeletal muscle *in vivo*.
4. Felgner and Rhodes (1991) *Nature* 349:351 provide an overview of numerous expression vectors and citations for studying the efficacy of certain delivery vehicles in certain tissues, *in vivo*.
5. Ulmer et al (1993) *Science* 259:1745 describe the study using expression vectors to assess the effect of viral antigens on generating a cytotoxic T Lymphocyte response (see page 1746, middle column).
6. Nabel et al (1995) *Ann N Y Acad Sci.* 772:227-31 describe the use of expression vectors to study the efficacy of direct gene transfer for treating cancer.
7. Wheeler et al (1996) *Proc. Natl. Acad. Sci, USA* 93:11454-11459 describe the use of expression vectors to assess the efficacy of cationic lipids as a delivery vehicle to a mouse lung.
8. Waddill et al (1997) AJR Am J Roentgenol.;169(1):63-7 describe the use of expression vectors to test the efficacy of using CT-guided interstitial injection in the treatment of melanoma. (See the Abstract, "Results" section and page 64column 1, 1st paragraph for a description of using an expression vector for this purpose).
9. Manthorpe et al (1993) Hum Gene Therapy 4:419-431 describe the use of an expression vector to assess the efficacy of gene expression in muscle tissue upon direct injection the vector into mouse muscle tissue.

10. Stephan et al (1996) Hum Gene Therapy 7:1803-1812 describe the use of an expression vector to assess the effect of cationic liposomes of gene delivery into arteries of Yorkshire pigs (see page 1805, col. 1).

11. San et al (1993) Hum Gene Therapy 4:781-788 describe the use of expression vectors to determine the safety and toxicity of cationic lipid formulation when used to deliver the expression vectors (see page 782, section "Animal studies").

12. Stopeck et al (1997) J Clin Oncol. 15(1):341-349 describe the use of expression vectors to "determine the safety, toxicity, and efficacy of direct intratumoral injection of an allogenic major histocompatability complex (MHS) class I gene, HLA-b7, in a cationic lipid vector (allovectin-7; Vical, Inc, San Diego, CA) in patients with metastatic melanoma." (Abstract, page 341).

13. Zhu et al (1996) Gene Therapy 3:472-476 describe the use of expression vectors to assess the efficacy of single and continuous injection of liposome complexes into a mouse brain tumor.

14. Rubin et al (1997) Gene Therapy 4:419-425 describe the use of expression vectors to "test the feasibility and toxicity of immunotherapy of hepatic metastases from colorectal carcinoma by direct gene transfer of HLA-B7" (Abstract, page 419).

15. Felgner (1998) Current Biology 8(16):R551-553 reviews the study of expression vectors as potential vaccines in, for example, mice.

16. Hersh et al (1994) Hum Gene Therapy 5:1371-1384 reviews the use of expression vectors to treat malignant melanomas via direct injection of the expression vector.

In view of the above, discussion and the attached publications, Claims 56-67 are unquestionably enabled within the meaning of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of this ground of rejection is requested.

Applicants also request that this application be passed onto issuance.

Respectfully submitted,

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